

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

Claims 1-21: Cancelled

22. (Currently amended) A method for ~~detecting~~ assaying an allele ~~via hybridization~~, comprising:

hybridizing a target oligonucleotide to oligonucleotides that are coupled to different bead sets to form a complex, wherein the oligonucleotides that are coupled to different bead sets are oligonucleotides with and without a spacer; and assaying the complex for specificity of different alleles.

23. (Previously presented) The method of claim 22 further comprising separating allele specific nucleic acid fragments.

24. (Previously presented) The method of claim 23 wherein separating allele specific nucleic acid fragments comprises using oligonucleotides for specific polymorphisms coupled to different bead sets.

25. (Currently amended) The method of ~~any one of claims~~ claim 22 further comprising coupling oligonucleotides for specific polymorphisms to different bead sets.

26. (Currently amended) The method of ~~any one of claims~~ claim 22 further comprising coupling oligonucleotides with and without a spacer to different bead sets.

27. (Currently amended) The method of ~~any one of claims~~ claim 22 further comprising obtaining a target nucleic acid sample containing multiple alleles, each allele having a unique set of heterosequence sites.

28. (Currently amended) The method of ~~any one of claims~~ claim 27 further comprising amplifying the target nucleic acid.

29. (Currently amended) The method of ~~any one of claims~~ claim 27 further comprising denaturing the target nucleic acid into single stranded nucleic acid.

30. (Currently amended) The method of ~~any one of claims~~ claim 22 further comprising confirming the sequence of the target oligonucleotide template by hybridizing the target oligonucleotide nucleic acid templates with a second bead set that is complementary to the target oligonucleotide template and measuring the hybridization ~~of the nucleic acid templates~~ by flow cytometry.

31. (Currently amended) The method of ~~any one of claims~~ claim 22 wherein the target oligonucleotide is an HLA allele.

32. (Currently amended) The method of ~~any one of claims~~ claim 22 wherein the bead sets that are coupled to the oligonucleotides with and without a spacer are conjugated with or attached to different oligonucleotides and can be identified by a fluorescence color ratio.

33. (New) The method of claim 22 wherein the spacer is nucleic acid bases.

34. (New) The method of claim 33 wherein the bases are random bases.

35. (New) The method of claim 22 wherein the spacer is in the middle of the oligonucleotide sequence.

36. (New) The method of claim 22 wherein the oligonucleotides that are coupled to different bead sets are selected to have perfect sequence homology to their respective target oligonucleotides.

37. (New) The method of claim 22 wherein each different oligonucleotide for a specific allele is coupled to a different bead set.

38. (New) The method of claim 22 wherein the different bead sets have different specific fluorescence color ratios.

39. (New) The method of claim 22 wherein the beads are fluorescent beads.

## **REMARKS**

Claims 22-39 are currently pending in the present application. Claim 22 has been amended to make the preamble language consistent with the language in the body of the claim. Claim 25-30 and 32 have been amended to correct typographical errors and to use consistent terminology in the claims. New claims 33-39 have been added.

Support for the new claims can be found throughout the application as originally filed, including:

Claim 33: Paragraph [0069];  
Claim 34: Paragraph [0069];  
Claim 35: Paragraph [0069];  
Claim 36: Paragraph [0068];  
Claim 37: Paragraph [0068];  
Claim 38: Paragraph [0074.15]; and  
Claim 39: Paragraph [0038].

The amendments to the claims are supported by the application as originally filed, do not add new matter, and are otherwise proper. Applicants respectfully request entry of this Amendment in its entirety. In view of the above amendment and following remarks, applicants respectfully request reconsideration of the claims and submit that the application is in condition for allowance. This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, are presented, with an appropriate defined status identifier. Because the amendments makes explicit what was inherent, broaden or do not narrow the scope of the claims, the claim amendments are not narrowing and the claims are entitled to the same scope either literally or under the Doctrine of Equivalents.

### **I. Information Disclosure Statement**

Applicant thanks the Examiner for indicating that the information disclosure statement submitted February 7, 2002 was considered in the present application. A supplemental

information disclosure statement was mailed in this application April 18, 2003. Applicant respectfully requests the Examiner provide applicant an initialed copy of the PTO form 1449 submitted with the supplemental information disclosure statement indicating that the references supplied therewith were considered by the Examiner.

## **II. Drawings**

In the Office Action the drawings were objected to for various informalities. Applicant submits herewith replacement drawing for original drawing sheets 1, 2, 2A, and 3, now drawing sheets 1, 2A, 2B and 3. Accordingly, applicant respectfully requests the Examiner withdraw the objections to the drawings.

## **III. Specification**

The Office Action also objected to the specification for various informalities. Applicant has amended the specification to correct typographical errors and address the objections to the specification. Applicant respectfully requests the Examiner withdraw the objections.

## **IV. Incorporation by Reference**

The Examiner indicated that the present application should be amended to include all essential material incorporated by reference. Applicant has amended the present application to include the examples set forth in the provisional application which the present application claims priority to and incorporates by reference. Enclosed herewith is a declaration of a practitioner representing the applicant that the amendatory material consists of the same material incorporated by reference in the referencing application. At this time, any material incorporated by reference, but not included in the present application, is not believed to be essential. Applicant reserves the right to amend the present application to include any material incorporated by reference that is considered to be essential.

**V. Claim Rejections – 35 U.S.C. §112**

A) In the Office Action, claim 22 was alleged to be indefinite because the claim “does not recite a final process step, which clearly relates back to the preamble.” Applicant has amended the non-limiting preamble of the claim to relate to the steps recited in the body of the claim.

B) Claim 22 was also rejected:

as indefinite over the recitation of ‘wherein the oligonucleotides that are coupled to different bead sets are oligonucleotides with and without a spacer...’. It is not clear whether the oligonucleotides with spacers are coupled to different bead sets than oligonucleotides with spacers, or whether each of the different bead sets has oligonucleotides with and without spacers coupled to it. In addition, it is not clear whether the differences between bead sets are determined by the presence or absence of the spacers in oligonucleotides coupled to beads.

Applicant respectfully submits that all combinations of oligonucleotides with and without spacers coupled to bead sets are permissible in the claimed invention so long as the claimed method can be effectively performed.

C) Claim 22 was rejected for reciting the phrase “‘assaying the complex for specificity of different alleles...’ It is not clear what is encompassed by this step, since it is not clear what it means to assay a complex for allele specificity or what ‘allele specificity’ means, since ‘specificity’ is a relative term. Applicant respectfully disagrees with this rejection because the skilled artisan clearly understands that allele specificity in a hybridization reaction refers to the degree of complementarity between an oligonucleotide and its target oligonucleotide. Additionally, one skilled in the art recognizes that such complementarity can be measured in any number of different ways, for example by hybridization, melting temperature, etc.

D) Claims 25-32 were rejected for reciting the phrase “any one of claims...” Applicant has deleted the terminology from the claims rendering the rejection moot.

E) In the Office Action claim 26 was rejected as “indefinite over the recitation of ‘coupling oligonucleotides with and without a spacer to different bead sets...’. It is not clear whether the oligonucleotides with spacers are coupled to different bead sets than

oligonucleotides without spacers, or whether each of the different bead sets has oligonucleotides with and without spacers coupled to it.” As discussed above, this language covers all permutations of coupling oligonucleotides with and without spacers to beads as long as the underlying method can be effectively performed.

F) Claim 27 was rejected as “indefinite over the recitation of ‘further comprising obtaining a target nucleic acid sample containing multiple alleles...’. It is not clear what is the relationship of the target nucleic acid sample to the target oligonucleotide of claim 22, and where in the method of claim 22 the step of claim 27 takes place.” Applicant respectfully submits that the phrase is not indefinite because the target nucleic acid sample potentially includes the target oligonucleotide of claim 22, provided of course the source of the sample has the target oligonucleotide. Additionally, the target nucleic acid sample would be obtained prior to or subsequent with nucleic acid hybridization.

G) Claim 30 was rejected as indefinite for lacking antecedent basis for the phrase “the template[.]” Claim 30 has been amended to recite “target oligonucleotide” in place of “template” or “nucleic acid templates” rendering the ground for rejection moot.

H) In the Office Action claims 32 was rejected as indefinite because “it is not clear what is encompassed by the limitation ‘different oligonucleotides’”. The term “different” in the present claims has been used in accordance with its usual and ordinary meaning of “not the same as[.]” MERRIAM WEBSTER’S COLLEGIATE DICTIONARY 323 (10th ed. 1997). As such, “different oligonucleotides” are oligonucleotides are oligonucleotides that are not the same as one another, meaning that they have different sequences, configurations or chemical constituents.

I) Claim 32 was alleged to be indefinite in the Office Action because “[i]t is not clear whether ‘can be identified’ refers to a property of the beads or to a method step of identifying the beads.” Applicant respectfully submits that the phrase refers to a property of the beads.

J) Claim 32 was also alleged to be indefinite because “it is not clear whether the phrase ‘conjugated with’ refers to a property of the beads or to a step of conjugation of the beads

to oligonucleotides.” Applicant has amended to the claim to make it clear that the claim can refer either to a step of conjugation of the beads to oligonucleotides or simply to oligonucleotides attached to the beads.

Because the claims “apprise[] one of ordinary skill in the art of [their] scope and, therefore, serve the notice function required by 35 U.S.C. §112, second paragraph” (MPEP §2173.02), applicant respectfully requests the Examiner withdraw these rejections.

#### **VI. Claim Rejections - 35 U.S.C. § 102**

In the Office Action, claims 22-29, 31 and 32 were “rejected under 35 U.S.C. 102(e) as being anticipated by Van Ness *et al.* (U.S. Patent No. 6,361,940 B1).” However, Van Ness *et al.* cannot anticipate any of the present claims because they fail to teach or suggest every element of the present claims. Specifically, Van Ness *et al.* cannot anticipate the present claims because they do not teach the spacer of the presently claimed methods. The spacer of the present claims is located internally to an oligonucleotide sequence that is generally complementary to a target oligonucleotide and does not replace any of the bases in the oligonucleotide sequence. As such, the present spacer not only lengthens the size of the molecule it also separates two portions of a single oligonucleotide sequence. The nucleotide residues that are adjacent to the ends of the present spacer are adjacent to each other when the oligonucleotide hybridizes with a target oligonucleotide.

In contrast, Van Ness *et al.* use a “specificity spacer” which replaces a portion of an oligonucleotide. Van Ness *et al.* clearly state “the base analog replaces a G, C, or T base in a probe or primer” and “base analogs... maintain essentially the ‘natural’ separation between adjacent nucleotides [and] have a moiety with approximately the same spatial requirements of a G, C, A, or T base.” Column 43, lines 46-47 and lines 34-38, respectively. See also, the sequence listing which states “N is an unnatural nucleotide (i.e., a nucleotide having a chemical moiety which is not one of A,G,C,T or U at the position normally occupied by A,G,C,T or U) or a molecular spacer that provides an equal linear distance, as a natural nucleotide, along the DNA phosphate sugar backbone.” Accordingly, Van Ness *et al.*’s specificity spacer does not change

the length of the molecule that includes the specificity spacer. Moreover, the nucleotide residues that are adjacent to the ends of the specificity spacer are separated from each other by the length of the specificity spacer when the oligonucleotide hybridizes with a target. Therefore, Van Ness *et al.* fail to teach or suggest all of the elements of the present invention and applicant respectfully requests the Examiner withdraw this rejection.

Regarding claims 32, 38 and 39 Van Ness fails to teach or suggest any assay that uses fluorescent beads. Although the Office Action stated that “Van Ness *et al.* teach oligonucleotides... coupled to different bead sets labeled with fluorescent labels such as BODIPY, TAMRA or Texas Red... (col. 83, lines 10-67)” Van Ness *et al.* make it clear in the cited example that the probe oligonucleotides, not the solid bead, is fluorescently labeled when they state “[e]ach probe oligonucleotide is labeled with either BODIPY, TAMRA or Texas Red.” Column 83, 29-30 (emphasis added). In fact, the fluorescently labeled probe oligonucleotide is not even immobilized on the solid support because only the “‘target’ oligonucleotide was immobilized on a set of solid supports.” Column 83, lines 19-21 (parenthetical omitted). Accordingly, the fluorescent label stays with the probe oligonucleotide and not the solid support, which Van Ness make clear when they state that the probe oligonucleotide was denatured and the “solution [containing the denatured, labeled probe] is removed from the incubation tubes and placed in a black microtiter plate. The plates are then read directly...” Column 83, lines 38-45 (parentheticals omitted). Accordingly, Van Ness *et al.* cannot anticipate any of the present claims as they fail to teach or suggest all of the claim elements and applicant respectfully requests the Examiner withdraw this rejection.

Van Ness *et al.* also cannot anticipate claims 32 or 38 because they further fail to teach or suggest bead sets that have a fluorescence color ratio. Because a ratio is a comparison between two different things, in order to have a fluorescence color *ratio* the bead of claims 32 or 38 is labeled with at least two different fluorescent labels. Nowhere do Van Ness *et al.* teach a fluorescently labeled bead, much less a bead with at least two fluorescent labels.



## VII. Claim Rejections - 35 U.S.C. §103

In the Office Action claims 22-29, 31 and 32 were rejected as obvious over Kaneoka *et al.* and Van Ness *et al.* In order to “establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art.” MPEP §2143.03. Based on this standard, the combination of Kaneoka *et al.* and Van Ness *et al.* cannot render the rejected claims *prima facie* obvious because this combination of references fails to teach or suggest all the elements of the rejected claims. As discussed above, Van Ness *et al.* fail to teach or suggest the present spacer configuration. Kaneoka *et al.* do not overcome this deficiency as even the Examiner admits that “Kaneoka *et al.* do not teach oligonucleotides with and without spacers coupled to different bead sets.” Accordingly, this combination of references cannot state a proper *prima facie* case of obviousness and applicant respectfully requests the Examiner withdraw this rejection.

Claim 30 was rejected as obvious in over Kaneoka *et al.* and Van Ness *et al.* further in view of Nolan *et al.* However, Nolan *et al.* cannot overcome the deficiencies of Kaneoka *et al.* or Van Ness *et al.* because they also fail to teach or suggest the claimed spacer arrangement. Accordingly applicant respectfully requests the Examiner withdraw this rejection.

Claims 22-29 and 32 were rejected in the Office Action as obvious over Armstrong *et al.* and Van Ness *et al.* As discussed above, Van Ness *et al.* does not teach all of the elements of the present claims. Armstrong *et al.* cannot overcome this deficiency because they “do not teach oligonucleotides with and without spacers” as admitted by the Examiner. Accordingly, this combination of references cannot render the rejected claims *prima facie* obvious and applicant respectfully requests the Examiner withdraw this rejection.


In the Office Action claim 31 was rejected as obvious over Armstrong *et al.* and Van Ness *et al.* further in view of Long. Neither Armstrong *et al.* nor Van Ness *et al.* teach or suggest the spacer configuration of the rejected claims. Long does not overcome this deficiency because they also fail to teach or suggest a spacer as presently claimed. Accordingly, applicant respectfully requests the Examiner withdraw this rejection.

**CONCLUSION**

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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